No. 17-290

In the Supreme Court of the United States

MERCK SHARP & DOHME CORP., PETITIONER

v.

DORIS ALBRECHT, ET AL.

ON WRIT OF CERTIORARI
TO THE UNITED STATES COURT OF APPEALS
FOR THE THIRD CIRCUIT

BRIEF FOR THE UNITED STATES
AS AMICUS CURIAE SUPPORTING PETITIONER

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QUESTION PRESENTED

Whether a state-law failure-to-warn claim alleging the insufficiency of brand-name drug labeling is preempted by the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 301 *et seq.*, when the Food and Drug Administration, after the drug manufacturer provided it with the relevant scientific data, rejected the manufacturer's application to modify its labeling to warn about the risk underlying the tort claim.

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INTEREST OF THE UNITED STATES

This case concerns the circumstances under which a decision of the Food and Drug Administration (FDA) rejecting proposed changes to the labeling of a brand-name drug preempts state-law tort claims that allege that the drug manufacturer failed to provide adequate warnings on its labeling. At the Court's invitation, the United States filed a brief as amicus curiae at the petition stage of this case.

STATEMENT

1. This case involves a series of tort claims alleging that petitioner's labeling for its Fosamax drug products insufficiently warned of the drugs' risks. Petitioner has argued, among other things, that many of the failure-to-warn claims are preempted because, in 2009, FDA rejected its attempt to strengthen relevant warnings on

that labeling. The regulatory scheme for drug labeling establishes the framework for that defense.

a. Congress has charged FDA with ensuring that each "drug is safe for use under the conditions prescribed, recommended, or suggested" in its "labeling." 21 U.S.C. 355(d); cf. 21 U.S.C. 321(m) (defining "labeling"); 21 U.S.C. 352(f) (misbranding). FDA regulations govern the content and format of prescription-drug labeling. See, *e.g.*, 21 C.F.R. 201.56, 201.57; see 21 C.F.R. 201.100(c). Those regulations are intended to organize labeling information to more effectively communicate to healthcare professionals the "information necessary for the safe and effective use of prescription drugs." 71 Fed. Reg. 3922, 3928 (Jan. 24, 2006). Two separate labeling sections now generally required on prescription-drug labeling are relevant here: the Warnings and Precautions section and the Adverse Reactions section. See 21 C.F.R. 201.57(c)(6) and (7).[1]

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[1] The specific requirements for labeling content and format discussed in the text generally apply to prescription drugs subject to a new drug application (NDA) or efficacy supplement approved on or after June 30, 2001. 21 C.F.R. 201.56(b)(1). The specific labeling requirements for older drug products differ in certain respects. See 21 C.F.R. 201.56(e), 201.80.

This case involves the labeling of three FDA-approved Fosamax products: Fosamax tablets (NDA 20560, approved 1995); Fosamax oral solution (NDA 21575, approved 2003); and Fosamax Plus D tablets (NDA 21762; approved 2005). See J.A. 510-511; see also FDA, *Approved Drug Products with Therapeutic Equivalence Evaluations* 3-12, 6-14 (38th ed. 2018) (listing Fosamax products). Although the newer labeling requirements discussed in this brief did not apply to all of those products at the time relevant here, no party has suggested that the differences between the two sets of labeling requirements are relevant to this case. The government agrees. This brief therefore follows the path taken by the court of appeals,

The Warnings and Precautions section must identify "clinically significant adverse reactions" and certain other safety hazards where "reasonable evidence of a causal association" between the drug and such hazards exists. 21 C.F.R. 201.57(c)(6); see 73 Fed. Reg. 49,603, 49,604 (Aug. 22, 2008) (stating that a "'preponderance' of evidence" is not required). FDA adopted that causal standard in part to "prevent overwarning" of potential risks, which, if included in the Warnings and Precautions section, could dilute other "more important warnings" or "deter appropriate use" of the drug. 73 Fed. Reg. at 49,605-49,606. FDA thus reserves this section for only a "discrete set" of hazards serious enough to affect prescribing decisions. FDA, *Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format* 3 (Oct. 2011), https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075096.pdf.[2]

The Adverse Reactions section, by contrast, describes "the overall adverse reaction profile of the drug." 21 C.F.R. 201.57(c)(7). The causal threshold for including an adverse reaction in this section is lower than that for the Warnings and Precautions section: An adverse reaction must be listed if "some basis" exists

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which based its decision on the newer labeling requirements in Section 201.57(c) without discussing Section 201.80. See Pet. App. 7a-9a & nn.6, 9-10, 16, 51a n.130, 63a-64a nn.154, 156.

[2] The 2011 guidance describes FDA's interpretation of its 2006 labeling regulations. FDA has informed this Office that the 2011 guidance accurately reflects how FDA treated the Warnings and Precautions section during the period relevant here.

"to believe there is a causal relationship between the drug and the occurrence of the adverse event." *Ibid.*

b. A brand-name drug "manufacturer bears responsibility for the content of its label[ing] at all times." *Wyeth* v. *Levine*, 555 U.S. 555, 570-571 (2009); see 21 U.S.C. 355(*o*)(4)(I). When new information becomes available about a new risk or a new aspect of a known risk that causes existing labeling to become inadequate, the manufacturer is responsible for pursuing a revision to its labeling. See 21 C.F.R. 201.57(c)(6)(i) (stating that updated warning must be added "as soon as" sufficient causal evidence of a clinically significant hazard exists); 21 C.F.R. 201.57(c)(7)(ii)(B) (requiring list of adverse reactions identified in postmarketing experience); cf. 21 C.F.R. 201.56(a)(2) (requiring updated labeling "when new information becomes available that causes the labeling to become inaccurate, false, or misleading").[3]

i. After FDA has approved a new drug application (NDA) for a drug, 21 U.S.C. 355(b)(1) and (d), two mechanisms exist for changing a brand-name prescription drug's labeling, both of which require that the manufacturer file a supplemental NDA for FDA approval. First, the sponsor may submit a Changes Being Effected (CBE) supplement for certain labeling changes, which allows the manufacturer immediately to implement its proposed labeling changes upon FDA's receipt of the supplement. 21 C.F.R. 314.70(c)(6) and (iii); see *Wyeth*, 555 U.S. at 571, 573. A CBE supplement may be submitted, for instance, to add or strengthen a warning,

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[3] Because a generic drug's labeling generally must track that of its reference listed drug, generic-drug manufacturers cannot independently change such labeling. See, *e.g.*, *Mutual Pharm. Co.* v. *Bartlett*, 570 U.S. 472, 486, 488 (2013); *PLIVA, Inc.* v. *Mensing*, 564 U.S. 604, 613-615, 618 (2011).

precaution, or adverse reaction to reflect "newly acquired information" if "the evidence of a causal association satisfies the [relevant] standard for inclusion in the labeling." 21 C.F.R. 314.70(c)(6)(iii)(A); see 21 C.F.R. 314.3(b) (defining "[n]ewly acquired information"). If FDA later disapproves the supplement, however, it may order the manufacturer to cease distributing the drug with the labeling changes. 21 C.F.R. 314.70(c)(7).

Second, the sponsor may submit a Prior Approval Supplement (PAS) to propose labeling changes. 21 C.F.R. 314.70(b) and (2)(v). Under that procedure, FDA approval is required before the changes are made. 21 C.F.R. 314.70(b)(3). A PAS "must be submitted" for certain types of changes that "include, but are not limited to," certain labeling changes other than those described in Section 314.70(c)(6)(iii) for CBE supplements. 21 C.F.R. 314.70(b)(1), (2), and (v)(A). Historically, FDA has also accepted PAS applications instead of CBE supplements, as occurred in this case, particularly where significant questions exist on whether to revise or how to modify existing drug labeling.[4]

ii. "All procedures and actions that apply to an application" submitted to FDA generally apply "to supplements." 21 C.F.R. 314.71(b) and (c). FDA has accordingly confirmed to this Office that it follows many of the general principles applicable to its review of an NDA when undertaking the more limited task of reviewing supplements that propose safety-related labeling changes. More specifically, FDA communicates with the applicant about "scientific, medical, and procedural issues that

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[4] Cf. FDA, *Guidance for Industry: Safety Labeling Changes—Implementation of Section 505(o)(4) of the FD&C Act* 7 (July 2013), https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM250783.pdf.

arise" in the course of its review. 21 C.F.R. 314.102(a). The "[d]evelopment of final labeling" generally is then "an iterative process between the applicant and FDA" involving a series of communications.[5] If FDA reviewers identify "easily correctable deficiencies" in a supplement, they will "make every reasonable effort to communicate [them] promptly to applicants." 21 C.F.R. 314.102(b). And if only "editorial or similar minor deficiencies in the [proposed] labeling" exist, FDA may approve the supplement on the condition that the applicant makes appropriate corrections and submits a copy of the final labeling before marketing the drug with that labeling. 21 C.F.R. 314.105(b).

FDA will reject a supplement, however, if the proposed labeling change is false or misleading or if it does "not comply with the requirements for labels and labeling in [21 C.F.R. P]art 201." 21 C.F.R. 314.125(b)(6) and (8). In such circumstances, FDA will send the applicant a "complete response letter." 21 C.F.R. 314.110(a). A complete response letter reflects FDA's "complete review of the data submitted" and "will describe all of the specific deficiencies that the agency has identified." 21 C.F.R. 314.110(a)(1) and (2).

2. a. Petitioner is the manufacturer of Fosamax, a brand-name drug that FDA approved in tablet form in

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[5] See Center for Drug Evaluation & Research, FDA, *CDER 21st Century Review Process: Desk Reference Guide* 37 (2014), https://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM218757.pdf; see also FDA, *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products* 21 (Apr. 2005), https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079748.pdf (addressing "communication between the FDA and applicants" during "labeling discussions").

1995 for the treatment of osteoporosis in postmenopausal women. Pet. App. 5a, 12a; see p. 2 n.1, *supra*. Evidence later began to emerge suggesting a connection between Fosamax and an increased risk of an unusual type of thigh-bone fracture known as an "atypical femoral fracture[]," which occurs with no or minimal external trauma and results in a complete fracture of the femur. Pet. App. 6a, 13a-14a. Petitioner kept FDA informed of those studies. *Id.* at 13a.

In June 2008, FDA informed petitioner that it was aware of reports regarding the occurrence of atypical femoral fractures in patients using bisphosphonates like Fosamax. C.A. App. A1935-A1936. FDA stated that it was "concerned about this developing safety signal" and asked petitioner to submit any information it had on the issue. *Ibid.* Petitioner promptly complied. Pet. App. 14a.

b. In September 2008, petitioner submitted three Prior Approval Supplements for its three Fosamax products that proposed changing the relevant labeling to address atypical femoral fractures in two respects. Pet. App. 14a-15a; see p. 2 n.1, *supra*.[6]

First, in the Adverse Reactions section (J.A. 715-729), petitioner proposed adding a reference to "low-energy femoral shaft fracture." J.A. 728; see Pet. App. 16a. Petitioner also proposed including a parenthetical cross-reference to direct readers to a discussion of "Low-Energy Femoral Shaft Fracture" proposed for the Warnings and Precautions section. J.A. 728 ("(see

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[6] Relevant portions of one of the PAS applications are available at J.A. 669-761; see C.A. App. A2697-A2928 (reproducing additional portions). FDA has confirmed to this Office that petitioner proposed the same relevant labeling language for each of its three Fosamax products.

PRECAUTIONS, Low-Energy Femoral Shaft Fracture)") (emphasis omitted).

Second, in the Warnings and Precautions section (J.A. 703-715), petitioner proposed adding a new subsection with an identical title: "Low-Energy Femoral Shaft Fracture." J.A. 707 (emphasis omitted); see Pet. App. 15a. That subsection stated that "[l]ow-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate-treated patients." J.A. 707. The proposed warning added that "[s]ome" of those fractures were "stress fractures (also known as insufficiency fractures)," and the remainder of petitioner's proposed text repeatedly referenced stress fractures. *Ibid.*[7]

Petitioner supported its applications with evidence regarding femoral fractures in Fosamax users. Pet. App. 16a; see, *e.g.*, J.A. 745-761; C.A. App. A2748-A2928. The applications stated, as relevant, that petitioner's use of the term "stress fracture" in connection with reports of "low-energy subtrochanteric/mid femoral shaft fractures" referred to an "insufficiency fracture" that occurs with no "identifiable external traumatic event." J.A. 746, 748; see J.A. 748-749, 751. The treatment data in the applications indicated that 91% of the fractures resulted in surgical intervention and the other 9% involved patients who sustained only "incomplete stress fractures." J.A. 753.

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[7] An "insufficiency f[racture]"—which can be associated with "osteoporosis"—is "a stress fracture that occurs during normal stress on a bone of abnormally decreased density"; it is thus different from the type of "stress f[racture]" experienced by athletes (a fatigue fracture) "caused by unusual or repeated stress on a bone." *Dorland's Illustrated Medical Dictionary* 710-711 (29th ed. 2000).

In May 2009, FDA issued a Complete Response Letter (J.A. 510-513) informing petitioner that FDA could not "approve the[] applications in their present form." J.A. 511; see Pet. App. 18a. FDA stated that it "agree[d] that atypical and subtrochanteric fractures should be added" to the Adverse Reactions labeling section. J.A. 511. FDA therefore recommended that petitioner modify its proposed text (J.A. 728) for that section to read "low energy femoral shaft and subtrochanteric fractures." J.A. 512. With respect to petitioner's Warnings and Precautions proposal, however, FDA determined that the "justification for the proposed [Warnings and Precautions] section language is inadequate." J.A. 511. The letter also stated that "[i]dentification of 'stress fractures' may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature" and that "[d]iscussion of the risk factors for stress fractures is not warranted and is not adequately supported by the available literature and postmarketing adverse event reporting." J.A. 511-512.

In June 2009, petitioner updated the Adverse Reactions section of its Fosamax labeling (J.A. 253, 267-274) using FDA's recommended text. J.A. 274; see J.A. 279. Petitioner then withdrew its three pending PASs, J.A. 654-655, and submitted new CBE supplements for that labeling change as the "quickest route to upd[illegible]e" its labeling, J.A. 657-658. FDA later approved these CBE supplements.[8]

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[8] See FDA, *Supplement Approval* 1-2 (Mar. 1, 2010), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/020560s051s055s057,021575s012s016s018ltr.pdf (NDA 20560/S-057 and 21575/S-018); FDA, *Supplement Approval* 1-2 (Mar. 1, 2010), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/021762s005s009sS010ltr.pdf (NDA 21762/S-010).

c. Nearly a year after its Complete Response Letter, and after reviewing additional data submitted by petitioner and other manufacturers, FDA issued a Safety Announcement in March 2010 (J.A. 519-522) stating that "FDA's review of these data did not show an increase in [a] risk [of atypical subtrochanteric femur fractures] in women using [bisphosphonates]," but that FDA was working with an outside expert task force to "gather additional information." J.A. 519-520 (stating that the data "ha[d] not shown a clear connection between bisphosphonate use and [that] risk"); see Pet. App. 19a.

On September 14, 2010, the task force completed its report, which identified an apparent association between long-term bisphosphonate use and certain atypical femoral fractures. Pet. App. 20a; see J.A. 523.

d. On October 13, 2010, after studying the report, FDA exercised its authority under 21 U.S.C. 355(*o*)(4) to initiate safety-based changes to Fosamax's labeling. See J.A. 526-527, 546 (FDA letter dated Oct. 13, 2010). Under Section 355(*o*)(4), the Secretary of Health and Human Services, acting through FDA, "shall promptly notify" a brand-name drug manufacturer as the "responsible person" for a drug "[i]f the Secretary becomes aware of new safety information that the Secretary believes should be included in the labeling of the drug." 21 U.S.C. 355(*o*)(4)(A); see 21 U.S.C. 355(*o*)(2)(A)(ii) (defining "responsible person"). Within 30 days, the manufacturer then must either submit a supplemental application to change the labeling or notify the Secretary that (and explain why) it believes that no change is warranted. 21 U.S.C. 355(*o*)(4)(B). The Secretary must "promptly review and act upon such supplement" and,

if the Secretary disagrees with the manufacturer's labeling proposal or disagrees with the manufacturer's view that no changes are warranted, the Secretary "shall initiate discussions" to reach agreement within 30 days regarding a labeling change. 21 U.S.C. 355(*o*)(4)(C) and (D). The Secretary may thereafter "issue an order directing" the manufacturer "to make such a labeling change as the Secretary deems appropriate to address the new safety information." 21 U.S.C. 355(*o*)(4)(E).

FDA announced its decision to the public by explaining that it was requiring bisphosphonate manufacturers to modify their labeling to include information regarding the risk of such fractures in, among other places, the Warnings and Precautions section. J.A. 246, 249. In a briefing to reporters, FDA's Deputy Director for the Office of New Drugs explained that the data that FDA had previously reviewed was insufficient to allow the agency to "tease out the association between [bisphosphonates] and these rare atypical fractures," but that the task force's September 2010 report had helped FDA "understand the[] fractures" better, "provide[d] more information that more closely associate[d] the[] atypical fractures with long-term bisphosphonate use," and persuaded FDA that such fractures were "more closely related to these drugs * * * than [FDA] previously had evidence for." J.A. 488-489, 493-494; see J.A. 486.

FDA's October 2010 letter invoking Section 355(*o*)(4) likewise notified petitioner that FDA "ha[d] become aware of a possible increased risk of atypical subtrochanteric and diaphyseal femoral fractures in patients taking bisphosphonates, including Fosamax," and that FDA now believed that new safety information about that risk should be included in Fosamax's labeling, in-

cluding changes to the Warnings and Precautions section. J.A. 527, 528-529. In response, petitioner proposed a labeling change that utilized the term "stress fractures." Pet. App. 22a. FDA thereafter struck those references from petitioner's proposal in the course of approving the labeling change because, an FDA employee explained, the term would suggest to most practitioners "a minor fracture" that "would contradict the seriousness of the atypical femoral fractures" at issue. J.A. 566, 606-607; see Pet. App. 22a-23a; cf. J.A. 547, 549-628 (redline showing FDA edits to petitioner's proposed labeling).

3. Over 1000 plaintiffs subsequently filed separate state-law tort actions against petitioner, alleging that they had sustained atypical femoral fractures caused by taking Fosamax. Pet. App. 4a, 23a. Although plaintiffs asserted an array of tort theories, they generally alleged that petitioner had failed to provide adequate warnings on its Fosamax labeling. *Id.* at 4a, 24a. The cases were consolidated for pretrial proceedings as a multidistrict litigation (MDL). *Id.* at 23a.

One bellwether case within the MDL was selected for trial on its failure-to-warn claim. Pet. App. 24a-25a & n.64. Petitioner moved for summary judgment on preemption grounds, but the district court did not immediately rule on the motion. *Id.* at 163a. After a jury rendered a verdict for petitioner on case-specific grounds, the court rendered a post-trial decision holding that the bellwether plaintiffs' failure-to-warn claim was preempted. *Id.* at 25a-26a, 153a-174a.

The district court subsequently extended that preemption holding to the other MDL cases in which the plaintiff was injured before September 14, 2010—the

date of the expert task force report—and granted judgment to petitioner in those cases. Pet. App. 152a; see *id.* at 113a-152a.

4. The court of appeals vacated and remanded. Pet. App. 1a-74a.

The court of appeals concluded that its impossibility-preemption analysis was controlled by this Court's decision in *Wyeth* v. *Levine*, *supra*, which the court viewed as teaching that a drug-focused failure-to-warn claim is preempted "where there is 'clear evidence that the FDA would not have approved a change' to the label," Pet. App. 32a-33a (quoting *Wyeth*, 555 U.S. at 571). See *id.* at 28a-55a. The court concluded that *Wyeth*'s "clear evidence" discussion "announce[d] a standard of proof" that is "synonymous with 'clear and convincing evidence'" and required proof showing it "is highly probable that the FDA would not have approved a change to the drug's label." *Id.* at 35a, 37a; see *id.* at 33a-37a. The court further concluded that the relevant preemption determination—which involves "predict[ing] how the FDA would have reacted in a hypothetical scenario" involving a new proposal to strengthen labeling warnings, *id.* at 51a-52a—is a factual determination for a jury, not a legal one for a court. *Id.* at 38a-55a.

Applying those principles, the court of appeals held that summary judgment should not have been granted to petitioner. Pet. App. 55a-74a. As relevant here, the court determined that a "reasonable jury" could conclude that petitioner could have revised the Warnings and Precautions section of its labeling before September 2010. *Id.* at 56a-57a, 67a. A jury, the court reasoned, could find that FDA's 2009 decision to reject petitioner's proposed revision to that section was not based on FDA's determination that the evidence at the

time was insufficient to indicate that Fosamax caused atypical femoral fractures, but rather was based on FDA's dissatisfaction with the proposal's use of the term "stress fractures," which medical practitioners might misunderstand to refer to fractures less serious than the femoral fractures in question, *id.* at 64a-66a. See *id.* at 59a-68a.[9]

SUMMARY OF ARGUMENT

Petitioner provided FDA with the relevant scientific data about Fosamax's risks and, in May 2009, FDA *rejected* petitioner's proposal to add a warning about atypical femoral fractures in the Warnings and Precautions section of Fosamax's labeling. The court of appeals erroneously rejected petitioner's impossibility-preemption defense to respondents' state-law failure-to-warn claims, based on its determination that preemption required petitioner to establish by "clear and convincing" evidence that FDA would have denied a CBE supplement, which the court deemed to be a factual question for a jury to decide. The proper focus here is on whether FDA's May 2009 decision embodied a determination by FDA that insufficient causal evidence existed to warrant strengthening the Warnings and Precautions section of the Fosamax labeling to address atypical femoral fractures. That is a question of law for a court to resolve, not a question of fact for a jury. Moreover, FDA's 2009 decision, construed in light of the governing regulatory regime, and FDA's subsequent

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[9] The court of appeals also concluded that the district court erred in granting summary judgment on claims based on the Adverse Reactions section of Fosamax's labeling before its 2009 revision, Pet. App. 69a-73a, and on non-failure-to-warn claims, *id.* at 74a.

actions show that petitioner could not have altered Fosamax's labeling until late 2010.

A. FDA's May 2009 Complete Response Letter is a legal document reflecting the agency's exercise of legal authority to adjudicate petitioner's regulatory labeling application. The meaning and effect of such agency action is a legal question within the exclusive province of a court. Indeed, courts have long been vested with authority to interpret agency action as a question of law. See, *e.g.*, 5 U.S.C. 706. Judges, rather than lay juries, are best suited to evaluate the scope of an agency's determination because judges are trained and experienced in construing legal documents and are far better equipped to understand agency decisions in light of the governing statutory and regulatory context. Vesting that legal construction in judges familiar with administrative law also fosters the type of interpretive uniformity appropriate when determining the scope and effect of federal agency action. That holds true even when subsidiary factual questions are relevant to the court's legal determination of the meaning and effect of agency action. Cf. *Markman* v. *Westview Instruments, Inc.*, 517 U.S. 370, 388-389 (1996).

B. The court of appeals concluded that *Wyeth* v. *Levine*, 555 U.S. 555 (2009), required a clear-and-convincing-evidence standard, Pet. App. 35a-37a, that a jury must apply in this case, *id.* at 38a-55a. But *Wyeth* addressed distinct circumstances and did not address how to determine the meaning and effect of an *actual* FDA labeling decision. The longstanding rule is that judges, not courts, interpret such agency action as a question of law. Nor does *Wyeth*'s passing reference to "clear evidence" alter the preponderance-of-the-evidence

standard that applies in civil actions involving monetary disputes between private litigants.

C. FDA's May 2009 Complete Response Letter, the relevant regulatory context, and the agency's subsequent actions concerning Fosamax demonstrate that FDA determined that existing information about atypical femoral fractures was insufficient to warrant a change to Fosamax's Warnings and Precautions section. The record amply demonstrates that petitioner could not have updated its labeling until late 2010. Accordingly, respondents' corresponding state-law failure-to-warn claims are preempted.

ARGUMENT

THE COURT OF APPEALS ERRED IN REJECTING PETITIONER'S PREEMPTION DEFENSE

The court of appeals erred in holding that a jury must determine whether FDA's May 2009 decision—which declined to approve petitioner's proposal to revise Fosamax's Warnings and Precautions section to warn against "[l]ow-energy fractures of the subtrochanteric and proximal femoral shaft," J.A. 707—preempted respondents' state-law failure-to-warn claims arising from that same type of injury. Where, as here, FDA renders a decision declining to approve a drug-labeling change, the interpretation of that administrative decision and its significance for a failure-to-warn claim are legal questions for a court to resolve, not factual questions for a jury. Moreover, because FDA's action prevented petitioner from modifying the relevant labeling before late 2010, the court of appeals erred in rejecting petitioner's impossibility-preemption defense.

A. Petitioner's Preemption Defense Turns On The Meaning And Effect Of FDA's 2009 Complete Response Letter, Which Are Legal Questions That A Court Must Resolve

"The question for 'impossibility' [preemption] is whether the private party could independently do under federal law what state law requires of it." *PLIVA, Inc.* v. *Mensing*, 564 U.S. 604, 620 (2011). A state-law failure-to-warn claim that rests on the contention that a drug manufacturer failed to provide adequate warnings on drug labeling is therefore preempted if, under federal law, the manufacturer could not have "independently" altered the labeling at the relevant time without FDA's "special permission and assistance." *Id.* at 618-619, 623-624 & n.8. As a general matter, a name-brand drug "manufacturer may only change a drug label after the FDA approves a supplemental application." *Wyeth* v. *Levine*, 555 U.S. 555, 568 (2009). When that is so, potential failure-to-warn claims are preempted.

Some failure-to-warn claims, however, are not preempted under the Court's formulation in *Mensing*. A manufacturer may in certain circumstances submit a CBE supplement, which, upon its receipt by FDA, "permits [the] manufacturer to make certain [safety-based] changes to its label[ing] *before* receiving the agency's approval." *Wyeth*, 555 U.S. at 568 (emphasis added); see pp. 4-5, *supra* (discussing CBE process). FDA may thereafter disapprove the supplemental application and order the manufacturer to cease distributing the drug with such labeling changes. 21 C.F.R. 314.70(c)(7). This Court has accordingly concluded that a brand-name drug manufacturer will establish an impossibility-preemption defense by sufficiently establishing that FDA "would not have approved [the relevant] change to

[the drug's] label[ing]" under its CBE regulation. *Wyeth*, 555 U.S. at 571; see *Mensing*, 564 U.S. at 624 n.8.

In this case, the court of appeals held that the relevant judicial task in resolving petitioner's preemption defense "is to predict how the FDA would have reacted" under the requirements of its "CBE regulation" "in a hypothetical scenario" involving "a different label amendment than the one it actually rejected in [its] May 2009 [Complete Response] letter." Pet. App. 51a-52a. That is incorrect. The threshold inquiry here is whether FDA's May 2009 decision embodied a determination by FDA that insufficient causal evidence existed to warrant strengthening Fosamax's Warnings and Precautions section to address atypical femoral fractures. If FDA's May 2009 decision did reflect such a determination, then petitioner has established an impossibility-preemption defense. And the meaning of FDA's Complete Response Letter is a question of law for a court to resolve, not a question of fact for a jury.

1. Courts, not juries, determine the meaning of federal agency decisions

A federal agency's written decision on a regulatory application is a legal document: an agency action that embodies the agency's exercise of legal authority to adjudicate the application. Cf. 5 U.S.C. 551(6) and (7) (defining agency adjudication). The meaning and effect of such agency action present legal questions within the exclusive province of a court.

When Congress enacted the Administrative Procedure Act (APA), 5 U.S.C. 551 *et seq.*, 701 *et seq.*, it specified that a "reviewing court shall * * * determine the meaning or applicability of the terms of an agency action." 5 U.S.C. 706. That provision reflects the longstanding view that "questions respecting the * * *

terms of any agency action" and the "application" thereof are "questions of law" and therefore matters for "courts * * * to decide." H.R. Rep. No. 1980, 79th Cong., 2d Sess. 44 (1946); see U.S. Dep't of Justice, *Attorney General's Manual on the Administrative Procedure Act* 108 (1947) (APA's review provision "restates the present law").

The legal nature of that inquiry is consistent with this Court's precedent addressing the meaning and effect of a prior judicial adjudication. When issues adjudicated in prior litigation are relevant to factfinding in a subsequent civil action, this Court has held that the question of "[w]hat issues were decided [in that prior] litigation is * * * a question of law" that the trial court must itself decide by examining relevant materials from the prior case. *Emich Motors Corp.* v. *General Motors Corp.*, 340 U.S. 558, 571-572 (1951). That holds true even where a jury must consider "the scope and effect of the former judgment on the case at trial." *Id.* at 572; see *id.* at 568. In such circumstances, the trial court must first determine the prior adjudication's scope and effect before "instruct[ing] the jury" on its legal determination. *Id.* at 571. Just as the scope of a prior judicial adjudication is a question of law for a court to decide, so too is the scope of a federal agency adjudication like the one at issue here.

No sound reason exists for treating the meaning and effect of an FDA administrative determination any differently. Judges, rather than lay juries, are best suited to evaluate the scope of an agency's determination, both because judges are trained and experienced in "[t]he construction of written instruments," *Markman* v. *Westview Instruments, Inc.*, 517 U.S. 370, 388 (1996), and because judges are far better equipped to understand and

interpret agency decisions in light of the governing statutory and regulatory context. Moreover, framing the decision as a question of law to be decided by judges familiar with principles of administrative law will foster the type of uniformity appropriate when determining the scope and effect of federal agency action. See *id.* at 390-391; *id.* at 391 (concluding that uniformity would "be ill served by submitting issues of document construction to juries"). Whether the agency action is a notice-and-comment regulation or something less formal like the adjudicatory decision at issue here, the meaning of agency action is a legal question that a court should decide. See, *e.g.*, *Sprietsma* v. *Mercury Marine*, 537 U.S. 51, 64-68 (2002); cf. *Perez* v. *Mortgage Bankers Ass'n*, 135 S. Ct. 1199, 1208 n.4 (2015) ("[I]t is the court that ultimately decides wh[at] a given regulation means.").

2. Factual findings necessary to interpret a federal agency decision are also matters for courts to resolve

In some contexts, disputed factual questions can be relevant to a court's legal determination of the meaning and effect of an agency decision. For example, if FDA rejected a labeling supplement on the ground that the information supporting it was insufficient to warrant a labeling change, the meaning and scope of that decision can depend on what information FDA had before it. Yet in tort litigation between private parties (which typically will lack compilation of an official administrative record for an FDA decision), litigants may dispute whether a drug manufacturer submitted all material data to FDA. In addition, to the extent that an agency decision read in the proper regulatory context is insufficiently clear, a private litigant might seek to submit extrinsic material to provide further context for interpreting the decision. Where consideration of such

material requires resolution of factual matters for a court to determine the meaning and scope of the agency decision, the court itself should resolve them.

This Court in *Markman* confronted analogous circumstances when it held that "the construction of a patent" is a "purely legal" issue "exclusively within the province of the court." 517 U.S. at 372, 391. The Court reasoned that "judges, not juries, are the better suited" for discerning the meaning of patent terms, even though factual questions involving "credibility determinations" are sometimes "subsumed" within the relevant analysis. *Id.* at 388-389. In other words, the "ultimate issue of the proper construction of a [patent] claim [is] treated as a question of law" for a court to decide, even though "subsidiary factfinding is sometimes necessary." *Teva Pharm. USA, Inc.* v. *Sandoz, Inc.*, 135 S. Ct. 831, 838 (2015). The same rationale applies here. To the extent extrinsic evidence may sometimes be relevant in litigation between private parties to determine the meaning and effect of FDA's agency action, the court's evaluation of such subsidiary facts does not alter the ultimate legal character of the inquiry or the court's exclusive authority to resolve it.

B. The Court Of Appeals Erred In Holding That, Under *Wyeth* v. *Levine*, A Jury Must Resolve Petitioner's Preemption Defense As A Factual Matter Subject To A Clear-And-Convincing-Evidence Standard

The court of appeals should have treated the interpretation of FDA's 2009 labeling decision as a legal question for the courts to decide. As explained further below, the basis for FDA's 2009 Fosamax labeling decision is properly determined as a matter of law from FDA's Complete Response Letter, read in the context of petitioner's underlying labeling supplement and the

governing regulatory framework and related FDA actions. See pp. 30-34, *infra*.

The court of appeals, however, concluded that petitioner's preemption defense presented a question of fact for a jury and this Court's decision in *Wyeth* v. *Levine*, *supra*, required petitioner to provide "clear evidence" from which a jury could find that FDA "would [have] reject[ed] [the] plaintiff's proposed warning" for Fosamax if petitioner had proposed that warning to FDA. Pet. App. 33a, 54a. In addressing that "hypothetical scenario," the court of appeals determined that a jury could reasonably conclude that "FDA rejected [petitioner's] proposed warning about femoral fractures in 2009 not because" FDA deemed the "causal link between Fosamax and fractures" to be insufficient, but because FDA was dissatisfied with petitioner's proposed text. *Id.* at 51a, 64a-65a. There was nothing "hypothetical" about FDA's *actual* 2009 decision in this case, and nothing in *Wyeth* addresses how courts should determine the meaning and effect of such actual agency action.

1. ***Wyeth did not address whether courts or juries should construe an actual FDA decision***

In *Wyeth*, this Court determined that a state-law failure-to-warn claim involving a brand-name drug was not foreclosed by the doctrine of impossibility preemption, because the drug manufacturer had a duty to ensure the adequacy of its own labeling and could have invoked FDA's CBE regulation to update its labeling promptly to provide additional warnings. 555 U.S. at 570-573. The Court recognized that "FDA retains authority to reject [a manufacturer's unilateral] labeling changes made pursuant to the CBE regulation," *id.* at 571, but it explained that Wyeth did "not argue" that

any actual FDA decision had "prohibited" it from strengthening its labeling, *id.* at 572.

The Court instead viewed Wyeth as arguing that FDA had "intended to prohibit it" from changing the labeling when FDA approved prior applications for the relevant drug, a contention that the state trial and supreme courts had rejected. 555 U.S. at 572 & n.5. Thus, without any relevant agency decision at hand, this Court stated that it would not conclude that it was impossible for Wyeth to comply with both federal and state requirements "absent clear evidence that the FDA *would not have approved* a change to [the] label[ing]" in question. *Id.* at 571 (emphasis added). In other words, the Court reasoned that Wyeth needed to make a clear showing that "FDA would have rescinded any change in the label" that Wyeth made through the CBE process in order to establish the impossibility of such a change. *Mensing*, 564 U.S. at 624 n.8. The Court concluded that Wyeth, which did "not argue" that it had provided FDA with an analysis of the "specific dangers" in question, had failed to show that "FDA would have prevented it from adding a stronger warning." *Wyeth*, 555 U.S. at 572-573.

Because *Wyeth* discussed the question whether FDA would have rejected a CBE labeling change *if* the manufacturer in that case had unilaterally made such a change to strengthen its labeling, *Wyeth* did not resolve how to determine the meaning and effect of an actual FDA decision rejecting a proposed labeling change. For that reason, the court of appeals erred in transplanting *Wyeth*'s discussion about the need for "clear evidence" of what FDA "would have [done]" to this context, which concerns the meaning and effect of what FDA *actually did*. This Court has long cautioned that

it is "often misleading" to transplant "[g]eneral expressions" from one opinion "to other facts" because every opinion must be "read in the light of the facts of the case under discussion." *Armour & Co.* v. *Wantock*, 323 U.S. 126, 133 (1944); see *Landgraf* v. *USI Film Prods.*, 511 U.S. 244, 265 (1994) (citing *Cohens* v. *Virginia*, 19 U.S. (6 Wheat.) 264, 399 (1821) (Marshall, C.J.)). *Wyeth* simply does not speak to the circumstances presented here.

2. Any factual findings necessary to resolve a preemption defense need only rest on a preponderance of the evidence

The court of appeals erroneously determined (Pet. App. 35a-37a) that *Wyeth* requires "a factual showing" of impossibility by "clear and convincing evidence" in order to establish a preemption defense. To the extent any factual disputes must be resolved to establish preemption, the proper standard of proof is a preponderance of the evidence.

a. The preponderance-of-the-evidence standard applies in "civil actions between private litigants unless 'particularly important individual interests or rights are at stake'" or a statute prescribes a different standard. *Grogan* v. *Garner*, 498 U.S. 279, 286 (1991); see *Microsoft Corp.* v. *i4i Ltd. P'ship*, 564 U.S. 91, 100-103 (2011) (interpreting patent statute to require clear-and-convincing evidence in certain contexts).[10] Accordingly,

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[10] The clear-and-convincing evidence standard applies when, for instance, the government seeks to terminate an individual's parental rights, *Santosky* v. *Kramer*, 455 U.S. 745, 769-770 (1982), or seeks to deprive an individual of liberty in involuntary commitment proceedings, *Addington* v. *Texas*, 441 U.S. 418, 433 (1979).

in a "typical civil case involving a monetary dispute between private parties," the preponderance standard applies because private litigants should "share the risk of error in roughly equal fashion." *Addington* v. *Texas*, 441 U.S. 418, 423 (1979); see, *e.g.*, *Rivera* v. *Minnich*, 483 U.S. 574, 576, 579 (1987) (action by mother to obtain child-support payments by establishing paternity).

This is a typical private civil action for money damages, and nothing warrants a higher standard of proof to resolve the preemption question here. The Court's preemption decisions do not suggest that a higher evidentiary showing would generally be required where resolution of factual issues is necessary to establish that a state-law duty conflicts with federal law. Although the Court has applied a presumption against implied conflict preemption, that presumption is a "*rule of construction* [that] rests on an assumption about congressional intent," *Arizona* v. *Inter Tribal Council of Ariz., Inc.*, 570 U.S. 1, 13 (2013) (emphasis added), not an evidentiary principle governing the standard of proof. Cf. *Microsoft Corp.*, 564 U.S. at 103 (noting that the existence of a presumption alone does not "establish[] the governing standard of proof"); Fed. R. Evid. 301 (evidentiary presumptions shift the burden of production unless a statute or rule provides otherwise).

b. The court of appeals based its "clear and convincing evidence" requirement on a single sentence in *Wyeth*, Pet. App. 35a & n.94, 37a, in which the Court stated that it "w[ould] not conclude that it was impossible" for Wyeth to strengthen a drug's labeling under the CBE process "absent *clear evidence* that the FDA would not have approved a change to [the] label," 555 U.S. at 571 (emphasis added). But *Wyeth* did not squarely address or definitively resolve the relevant standard of proof

with the phrase "clear evidence." Cf. Pet. App. 28a, 33a-35a (characterizing *Wyeth*'s discussion as "cryptic"). *Wyeth* provides no analysis or any citation to suggest the Court believed it was imposing a higher burden of proof with respect to factual issues, and *Wyeth*'s passing reference to "clear" evidence is not properly read to require one.

This Court has used the term "clear evidence" in contexts in which the Court analyzes preemption issues as a question of law, reflecting an *interpretive* presumption against preemption. See, *e.g.*, *Geier* v. *American Honda Motor Co.*, 529 U.S. 861, 885 (2000) (noting that "a court should not find pre-emption too readily in the absence of clear evidence of a conflict"); *English* v. *General Elec. Co.*, 496 U.S. 72, 86 (1990) ("[W]e find no evidence of a 'clear and manifest' intent on the part of Congress to pre-empt tort claims like petitioner's."). The Court has also held that its use of the even more specific phrase "clear and convincing evidence" in another context involving a question of law should *not* be understood in its "strict evidentiary sense," but merely as a "useful reminder" that a general presumption concerning a *legal interpretation* should control if substantial doubt exists about "congressional intent." *Block* v. *Community Nutrition Inst.*, 467 U.S. 340, 350-351 (1984). The Court in *Wyeth* appears to have similarly used the phrase not as a shorthand for a formal clear-and-convincing evidentiary standard, but merely to indicate that a manufacturer asserting preemption must show that a labeling change was not warranted under the relevant statutory and regulatory framework. If the Court had intended to depart from the preponderance standard that applies to factual issues in almost all

civil actions between private litigants, it presumably would have explained such an unusual departure.

3. Resolving this case does not require factual findings

a. As the case comes to this Court, the preemption question is limited to a situation in which FDA considered the "relevant scientific data" in a prior labeling decision, Pet. i. See Gov't Cert. Amicus Br. 19 n.10; see also Pet. Br. 35 (discussing Sup. Ct. R. 15.2). This case is therefore properly resolved solely on the basis of a legal interpretation of FDA's 2009 labeling decision in light of the governing regulatory regime and subsequent FDA action. Respondents argue (Br. in Opp. 26) that, because petitioner relied below on an internal company document describing a telephone conversation with an FDA employee about petitioner's proposed labeling change, see Pet. App. 17a; J.A. 764-767, a factfinder should assess the reliability and weight of that evidence. But assuming that it would be appropriate to rely on such material in interpreting an agency decision, as explained above (pp. 20-21, *supra*), such a subsidiary factual question would be for courts to resolve in construing the meaning of FDA's 2009 decision; and as explained below (pp. 30-34, *infra*), there is in any event no need here for resort to such evidence because the meaning of FDA's 2009 decision is clear.

To be sure, an actual FDA labeling decision might not in itself resolve preemption if, for instance, FDA did not consider certain safety information in approving name-brand drug labeling or in denying a labeling change because the information was not provided to FDA or because it arose after FDA's decision. In such a situation, a plaintiff could argue that information that FDA did not consider constitutes "newly acquired information," 21 C.F.R. 314.3(b), 314.70(c)(6)(iii)(A), showing

that the drug caused a sufficiently serious hazard to have allowed the manufacturer to update its labeling under the CBE process. Cf. pp. 3-5, *supra*.[11] The proper adjudication of such a contention would need to account for the meaning and scope of any prior FDA labeling decision and the information that FDA previously evaluated in light of the governing statutory and regulatory scheme (matters that the court must resolve, see pp. 18-21, *supra*) in order to determine whether any arguably new information is materially different from the information that FDA previously determined to be insufficient. This case, however, does not present that question.

b. Respondents incorrectly analogize (Br. in Opp. 26; Supp. Cert. Br. 11) this case to *Boyle* v. *United Technologies Corp.*, 487 U.S. 500 (1988). In *Boyle*, this Court discussed the jury's role in evaluating whether a military contractor could raise a federal-common-law defense to a state-law design-defect claim. *Id.* at 504, 507-508, 514; see *Buckman Co.* v. *Plaintiffs' Legal Comm.*, 531 U.S. 341, 347 (2001) (describing *Boyle*). That defense required the contractor to make three factbound showings: (1) the United States approved reasonably

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[11] Information—including "new analyses of previously submitted data"—will qualify as "[n]ewly acquired information" only if it "reveal[s] risks of a different type or greater severity or frequency than previously included in submissions to FDA." 21 C.F.R. 314.3(b). Accordingly, nominally "new" information concerning risks of a materially similar type, severity, and frequency as those revealed in information previously evaluated by FDA is cumulative and not "newly acquired information" that could justify a CBE supplement. If for instance, FDA previously determined that that evidence of X was insufficient to warrant a warning about risk Y, the existence of additional but similar information about X would be insufficient to justify a warning.

precise specifications; (2) the allegedly defective military equipment conformed to those specifications; and (3) the contractor warned the United States about the dangers in the use of the equipment that were known to the contractor but not to the United States. *Boyle*, 487 U.S. at 512. In that context, the Court concluded that "whether the facts establish the conditions for the defense is a question for the jury," and it "would be error" for a reviewing court to itself determine that "the defense had [not] been established" unless "no reasonable jury" could have found that "that the Government contractor defense was inapplicable." *Id.* at 514.

Boyle, like *Wyeth*, did not involve the interpretation of an actual federal agency decision. *Boyle* thus does not address the key question here: whether the interpretation of FDA's 2009 decision is a legal inquiry for a court. Nor did *Boyle* address whether a jury should resolve the ultimate matter of preemption when preemption turns on the application of a complex regulatory regime implemented by an expert federal agency like FDA. Cf. *Riegel* v. *Medtronic, Inc.*, 552 U.S. 312, 325 (2008) (observing that a jury that "sees only the cost" of an FDA-approved product in a lawsuit about a plaintiff's injuries is unlikely to "apply cost-benefit analysis similar to that applied by the experts at the FDA"). Certainly, *Boyle* did not hold that the ultimate matter of preemption must always rest with a jury when the parties dispute what might be characterized as underlying factual issues. That question, which is not presented here, warrants further development in the lower courts once this Court has clarified that the preemptive effect of federal agency decisions involves legal questions for courts rather than juries.

C. FDA's May 2009 Decision Rejected A Change To Fosamax's Warnings And Precautions Because The Data At That Time Was Insufficient To Justify A Change

FDA's May 2009 decision rejecting petitioner's proposal to modify Fosamax's Warnings and Precautions section to address atypical femoral fractures was based on the agency's determination that the information about that risk was then insufficient to justify such a warning. That conclusion flows directly from the terms of the agency's May 2009 Complete Response Letter, the relevant regulatory context, and the agency's subsequent actions. Given FDA's determination, respondents' claim that petitioner should have updated its Warnings and Precautions labeling before late 2010 is preempted.

FDA's Complete Response Letter (J.A. 510-513) shows that FDA determined that the existing data for atypical femoral fractures was sufficient to update Fosamax's Adverse Reactions section, but not its Warnings and Precautions section. FDA determined that "atypical and subtrochanteric fractures should be added" as adverse reactions, J.A. 511, reflecting that FDA found "some basis to believe there [wa]s a causal relationship between the drug and the occurrence of th[at] adverse event." 21 C.F.R. 201.57(c)(7).

Petitioner's proposed addition to the Warnings and Precautions section was based on the *exact same risk*. Petitioner proposed a title ("Low-Energy Femoral Shaft Fracture") for its proposed subsection in Warnings and Precautions, J.A. 707, that was identical (with only differing capitalization) to its proposed text for the Adverse Reactions section, J.A. 728. The proposed warning for "[l]ow-energy fractures of the subtrochanteric and proximal femoral shaft," J.A. 707, likewise

addressed the same type of adverse reaction that FDA concluded should be added to Fosamax's labeling. See J.A. 512 (FDA's recommendation to add "low energy femoral shaft and subtrochanteric fractures" to Adverse Reaction section). And because both proposed labeling additions addressed the same risk, petitioner proposed adding an explicit cross-reference in the labeling's Adverse Reactions section ("[S]ee PRECAUTIONS, Low-Energy Femoral Shaft Fracture," J.A. 728) that would have directed readers to the more fulsome description of the same hazard proposed for the Warnings and Precaution section.

Under the governing regulations, however, such an adverse reaction is to be elevated to the Warnings and Precautions section only if "reasonable evidence of a causal association with [the] drug" exists. 21 C.F.R. 201.57(c)(6)(i). Here, FDA rejected petitioner's addition because the "*justification* for the proposed [Warnings and Precautions] section language [wa]s inadequate." J.A. 511 (emphasis added). Petitioner had also proposed stating that "[s]ome" of the reported fractures were "insufficiency" "stress fractures," J.A. 707. See p. 8 & n.7, *supra*. But FDA determined that such fractures "may not be clearly related to the atypical subtrochanteric fractures * * * *reported in the literature*," and the associated discussion of stress-fracture risk factors was likewise "not adequately *supported by the available literature and post-marketing adverse event reporting*." J.A. 511-512 (emphases added). FDA's decision thus was based on the lack of adequate data to support a warning.

The court of appeals focused instead on the possibility that "FDA [might have] rejected [petitioner's] proposed warning" because of the warning's use of the term

"stress fractures." Pet. App. 64a-65a. But a Complete Response Letter reflects "FDA's complete review of the *data* submitted"; and FDA's regulations make clear that the letter need not address any "proposed product labeling" if FDA determines that the "data submitted are inadequate." 21 C.F.R. 314.110(a)(2) and (3) (emphasis added). By contrast, if FDA determines that a safety-based labeling change is warranted based on the data, FDA will attempt promptly to identify easily correctable deficiencies in the proposed text and will develop final labeling text with the manufacturer in an iterative process. See pp. 5-6, *supra*. As a result, the May 2009 letter embodies FDA's "recommend[ation]" that petitioner modify its proposed Adverse Reactions text with language (shown here in italics) that FDA itself proposed: "low energy femoral shaft *and subtrochanteric* fracture*s*." J.A. 512 (emphasis added); cf. J.A. 728 (petitioner's proposal). FDA made no similar suggestions for revisions to petitioner's proposed addition in the Warnings and Precautions section because no warning was justified based on the information at the time.

That understanding is reinforced by FDA's subsequent actions in late 2010, when it concluded that the Warnings and Precautions section should be revised. FDA personnel directly edited petitioner's proposed language to remove stress-fracture references deemed insufficiently clear. Pet. App. 22a-23a; see J.A. 547, 549-628 (email with redline showing FDA edits to petitioner's proposed labeling); J.A. 606-607 (FDA edits to proposed warning about atypical subtrochanteric and diasphyseal femoral fractions). No sound basis thus exists for concluding that FDA determined in May 2009 that the data was sufficient to warrant a warning but

that it rejected petitioner's proposal because of petitioner's proposed text. Cf. *Dolin* v. *GlaxoSmithKline LLC*, No. 17-3030, 2018 WL 4001208, at *9 (7th Cir. Aug. 22, 2018) (concluding that it would be "unreasonable" to conclude that FDA rejected a proposed warning because the manufacturer had proposed adding it to the wrong place in the labeling, rather than because FDA had concluded that the warning was not warranted).

Significantly, FDA's own regulations require that the Warnings and Precautions section "must be revised" to add such a clinically significant hazard "*as soon as*" sufficient causal evidence exists. 21 C.F.R. 201.57(c)(6)(i) (emphasis added). And if FDA had "believe[d]" in May 2009 that the "new safety information" that petitioner had submitted "should [have] be[en] included in [Fosamax's] labeling," Section 355(*o*)(4) would have required that FDA "promptly notify" petitioner, 21 U.S.C. 355(*o*)(4)(A), and engage in expedited discussions to revise the labeling, 21 U.S.C. 355(*o*)(4)(B)-(D). Given the statutory and regulatory framework, it would not be reasonable to interpret FDA's 2009 decision as reflecting a determination that a new warning was justified but that FDA rejected petitioner's proposed warning because petitioner's proposed text was inadequate.

Indeed, nearly a year later, in March 2010, FDA announced—after reviewing further information—that it had yet to identify an "increase in [a] risk [of atypical subtrochanteric femur fractures] in women using [bisphosphonates]." J.A. 520. It was only in October 2010—after an external task force had completed its report on the issue—that FDA came to "believe that the information" about atypical femoral fractures should be added to the Warnings and Precautions section and

therefore invoked Section 355(*o*)(4) to revise the labeling for Fosamax and other bisphosphonates. See J.A. 527-528; see also pp. 10-12, *supra*.

In short, FDA's 2009 Complete Response Letter rejecting petitioner's PAS proposal to update Fosamax's Warnings and Precautions section, when read in the proper context of the governing statutory and regulatory regime—as well as FDA's subsequent regulatory actions regarding Fosamax—demonstrate that, in FDA's judgment, an update to Fosamax's Warnings and Precautions section to discuss atypical femoral fractures would not have been called for before late 2010. Accordingly, it would have been impossible under federal law for petitioner to provide such a warning at an earlier time. Any state-law failure-to-warn claim predicated on a state-law duty to provide such a warning is therefore preempted.

CONCLUSION

The judgment of the court of appeals should be reversed and the case remanded for further proceedings.

Respectfully submitted.

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* Solicitor General Noel J. Francisco is recused from this matter.

** General Counsel Robert P. Charrow is recused from this matter.